

Are pan-immune inflammation-value, systemic inflammatory response index clinically useful to predict in patients with chronic spontaneous urticaria?

Are inflammatory indexes important in patients with CSU?

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Abstract

Aim: Recent studies show that the immune inflammatory response plays an important role in chronic spontaneous urticaria (CSU). The aim of the study was to examine whether pan-immune inflammation value (PIV) and systemic inflammatory response index (SII) are effective in predicting CSU.

Material and Methods: Sixty-five patients and 65 healthy controls followed in the Allergy and Immunology Clinics of Ordu University Training and Research Hospital were included in this retrospective study.

Results: Neutrophil and lymphocyte, MPV, PDW, PCT and CRP levels were statistically significant between the patient and healthy controls ($p < 0.05$). A statistically significant difference was found in PLR, dNLR, SIRI and PIV indices between the groups ($p < 0.05$). We concluded that SIRI and PIV could be novel cost-effective biomarkers in patients with CSU.

Discussion: SIRI and PIV levels were statistically significant in patients with CSU. SIRI and PIV are newly designed indexes that are accepted as easily calculable and comprehensive indicators of immune response and systemic inflammation. Inflammatory indices can be an inexpensive, practical and safe indicator of the inflammatory state in patients with CSU.

Keywords

Chronic Spontaneous Urticaria, Inflammation, Systemic Inflammatory Response Index, Pan-Immune-Inflammation Value

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Introduction

Urticaria is defined as a heterogeneous inflammatory disease characterized by skin swelling, angioedema and blisters, which can be seen in two types as acute and chronic [1]. Chronic spontaneous urticaria (CSU) is defined as the presence of urticaria on most days of the week, characterized by an acute phase response and lasting more than six weeks and occurs in approximately 1% to 2% of the general population [2, 3]. The pathogenesis of chronic urticaria has not been fully elucidated, and it has been reported that one of the main causes of the disease is autoimmunity and the stress experienced in daily life plays an important role in the pathogenesis [4].

Oxidative stress (OS) occurs as a result of an abnormal increase in free radicals, resulting in a decrease in the effectiveness of antioxidant defense mechanisms, and the deterioration of OS balance [5]. As a result of the deterioration of the OS balance, an increase in proinflammatory cytokines occurs and this situation can make the inflammatory state worse by changing the enzymatic functioning [6, 7]. The symptoms seen in patients with CSU are usually attacks of angioedema and swelling of the dermal and mucosal tissues due to the activation of skin mast cells and the release of related mediators. This leads to the degranulation of skin mast cells with the formation of platelet-activating factors and arachidonic acid metabolites. The resulting metabolites activate sensory nerve endings that cause vasodilation, increased vascular permeability, swelling, flushing, and itching [8]. Although a very small population is affected by CSU, its prevalence is increasing day by day. CSU generally affects women more than children and men, and it seriously affects the quality of life and emotional well-being of patients [1, 9].

Inflammation is known to be associated with CSU and has been shown to be associated with many other diseases [3, 10, 11]. Moreover, inflammatory indices such as neutrophil-lymphocyte ratio (NLR), thrombocyte-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), Systemic inflammatory response index (SIRI) and pan-immune-inflammation value (PIV) have been shown in studies as potential indicators of systemic inflammation to predict prognosis and treatment response [11-14].

In the literature, SIRI and PIV are newly two designed immune biomarkers indices and are considered to be comprehensive markers of immune response and systemic inflammation due to their availability and cost-effectiveness. Recent studies state that SIRI and PIV are markers of systemic inflammatory conditions in many studies such as cancers, hypoxic-ischemic encephalopathy, acute pancreatitis, respiratory distress syndrome [15-18]. The aim of the study was to evaluate the effectiveness of the NLR, PLR, SII, SIRI and PIV together in patients with CSU.

Material and Methods

This retrospective study was conducted at Ordu University, Education and Research Hospital Department of Immunology and Allergic Diseases Outpatient Clinic from June 2022- to March 2023. A total of 65 patients diagnosed with CSU were included in the present study. The control group consisted of age and gender- matched healthy individuals. There was no

significant difference between the groups in terms of age and gender. The data of the study groups were obtained from the hospital automation system. The current study was approved by the ethics committee of Ordu University (Date: 31.03.2023 / No: 2023/86). The study was conducted in accordance with the Helsinki Declaration rules.

Patients with active infection, malignancy, diabetes mellitus, severe systemic disease, nutritional deficiency, malnourished, hematologic disease and on immunosuppressive, and other treatments of urticaria except for anti-histamines were excluded from the present study.

The hemogram parameters and serum C-reactive protein (CRP) levels were assessed. Neutrophil, lymphocyte, platelet and monocyte levels of groups were used in complete blood parameters. NLR, PLR, LMR, SII, SIRI PIV and dNLR respectively, were calculated as follows: the ratio of neutrophils to lymphocytes, platelets to lymphocytes, lymphocytes to monocytes, that of platelets x (neutrophils / lymphocytes), (neutrophils x monocytes)/lymphocytes and (neutrophils x platelets x monocytes) / lymphocytes. The neutrophil count was divided by the result of the WBC count minus the neutrophil count.

Statistical analysis

Data analysis of the groups was performed using the statistical software IBM SPSS 22. The normality of the quantitative variables was confirmed by using the Kolmogorov-Smirnov test. Comparative analysis of study groups was carried out with Student's t test and Mann-Whitney U (variables without normal distribution) test. Categorical variables were presented as numbers and percentages and compared with the chi-square test. The statistical significance level of the p-value was accepted as <0.05.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The present study consisted of a total of 65 subjects and 65 healthy controls with an average age of 41.4 ± 12.6 years and 65 CSU patients with an average age of 42.4 ± 14.1 years. There was no statistically significant difference between the groups in terms of age and gender (Table 1).

Median (min-max) outcomes of the hemogram parameters and indexes between the groups are shown in Table 2.

Neutrophil and lymphocyte, MPV, PDW, PCT and CRP levels were statistically significant between patients and healthy controls. In addition, inflammatory indices were calculated for the study groups. A statistically significant difference was found between PLR, dNLR, SIRI and PIV indices between the groups (p<0.05). Table 2). However, monocyte, hemoglobin and platelet, values were not significant between the patient and control groups (p>0.05).

Table 1. Demographic information of the study groups.

Parameters	CSU (n=65) Mean ± SD	Control (n=65) Mean ± SD	P
Gender	Male	18 (27.7%)	0.26*
	Female	47 (72.3%)	
Age (year)	42.4 ± 14.1	41.4 ± 12.6	0.68 [†]

*Chi-Square test, [†]Student t-test; CSU: chronic spontaneous urticaria

Table 2. Comparison of blood parameters of the study and control groups.

Parameters	CSU (n=65) median (min-max)	Control (n=65) median (min-max)	p*
White Blood Cell (10 ⁹ /L)	7.5 (4.2- 11.8)	7.4 (4.4-10.3)	0.456
Neutrophil (10 ⁹ /L)	4.3 (1.5- 8.3)	3.6 (2.3-6.9)	0.002
Lymphocyte (10 ⁹ /L)	2.4 (1.2- 4.3)	2.1 (1.1- 3.9)	0.037
Monocyte (10 ⁹ /L)	0.51 (0.27-1.46)	0.48 (0.23-1.06)	0.549
Hemoglobin (g/dL)	13.5 (9.9- 17.1)	13.2 (10.4 -17.7)	0.208
Platelet (10 ⁹ /L)	262 (152-402)	247 (162-438)	0.771
MPV (fL)	10.3 (8.4 -12.4)	9.3 (5.9 -12.1)	<0.001
PDW	11.9 (8.6-17.9)	8.9 (5.4-16.1)	<0.001
PCT	0.27 (0.14-0.37)	0.28 (0.17-0.59)	0.102
CRP (mg/L)	2.6 (0.3- 20.9)	1.6 (0.13-15.0)	0.010
SII	458.6 (146.7-1093)	439.1 (208.3-1036)	0.310
SIRI	0.86 (0.24-3.89)	0.73 (0.35-1.7)	0.013
PIV	245.0 (58.7-1121)	193.9 (85.6-580.3)	0.029
NLR	1.74 (0.6-4.1)	1.67 (0.85-3.4)	0.604
PLR	107.4 (61.4 -270.8)	95.3 (46.2- 138.2)	0.001
LMR	4.6 (1.8- 9.7)	4.5 (0.12-10.2)	0.753
dNLR	1.30 (0.3-5.3)	1.0 (0.32-11.3)	0.003

*Mann-Whitney U test, PCT: Procalcitonin, PDW: Platelet Distribution Width, NLR: Neutrophil-to- Lymphocyte Ratio, CRP: C-reactive protein, MPV: Mean Platelet Volume, PLR: Platelet-to- Lymphocyte ratio, dNLR: Derived NLR ratio (neutrophil count divided by the result of WBC count minus neutrophil count), SII: Systemic inflammatory index (neutrophil × platelet / lymphocyte count), SIRI: Systemic inflammatory response index (neutrophil × monocyte / lymphocyte count) and PIV: Pan-immune inflammation value (neutrophil × platelet × monocyte / lymphocyte count). CSU: chronic spontaneous urticaria

Discussion

This is the first report to investigate new inflammatory indexes such as NLR, PLR, LMR, SII, SIRI, and PIV together in patients with CSU. In this study, we examined the role of systemic inflammatory indices (SII, SIRI, PLR, NLR) in predicting the prognosis of patients with CSU. In the present study, neutrophil and lymphocyte, MPV, PDW, PCT and CRP levels were statistically significant between patients and healthy controls. Moreover, among the inflammatory indices, PLR, dNLR, SIRI and PIV were statistically significant between the patient and control groups. However, NLR and LMR were not found to be significant between the groups.

Based on the extant literature, there are many studies examining the effect of systemic inflammatory index on several diseases. In the study by Varghese et al. they observed that significant systemic inflammation increased hs-CRP and IL-18 levels in patients with chronic urticaria [4]. They concluded that systemic inflammation also increased disease severity and autoimmune diseases. Another study by Rajappa et al showed that systemic inflammatory markers are increased in CSU patients [19]. They think that the increase in the systemic inflammatory index is related to the severity of the disease. In addition, Dilivio et al. showed an increase in inflammatory biomarkers in their study of patients with CSU [20]. They reported that this increase is due to the increase in depression in CSU patients.

In our study, we observed higher levels of the inflammatory index in patients with CSU compared to the healthy controls. These findings are consistent with those of previous studies conducted on patients with CSU. In the present study, we evaluated the prognostic effect of SIRI and PIV in patients with CSU. SIRI and PIV levels were statistically significant in

patients with CSU. There is no study in the literature examining the prognostic effect of SIRI and PIV levels together with in patients with CSU.

SIRI and PIV are newly designed indexes that are accepted as easily calculable and comprehensive indicators of immune response and systemic inflammation. SIRI and PIV have been shown as biomarkers in different types of cancer and cardiovascular events [21, 22]. Tarkowski et al. indicated that there was no significant difference in SII, SIRI, PLR and NLR levels in patients receiving CSU treatment with Omalizumab [23]. They concluded that SIRI and PIV could be novel cost-effective biomarkers and treatment response precursors.

Ataseven et al. reported that WBC, NEU, PLT levels were statistically significantly higher than the healthy group in their study in patients with CSU [24]. However, they could not detect a significant difference between the groups in NLR and PLR levels. In our study, PLR levels were found to be significantly different in the two groups ($p < 0.05$). However, NLR levels were not found to be significant between the groups ($p > 0.05$). Acer et al. reported that they found NLR and PLR levels to be statistically significantly higher in the pre-treatment group in a comparative study before and after medication in chronic urticaria patients [25]. They concluded that drug use may have anti-inflammatory effects in patients with CSU.

Conclusion

As a result, SII, SIRI and PIV are new and practical inflammatory indices that can be used in the evaluation of CSU patients. These indices can be an inexpensive, practical and safe indicator of the inflammatory state in patients with CSU. However, a larger patient population is needed to obtain stronger results.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest.

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